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CLINICAL REVIEW

Blood pressure regulation, autonomic control and sleep disordered breathing in children

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SUMMARY

Sleep disordered breathing (SDB) ranges in severity from primary snoring (PS) to obstructive sleep apnoea (OSA). In adults, SDB is associated with adverse cardiovascular consequences which are mediated, in part, by autonomic dysfunction. Although SDB is common in children, fewer paediatric studies have investigated these cardiovascular effects. Initial research focused on those with OSA, indeed children with PS were occasionally utilised as the comparison control group. However, it is essential to understand the ramifications of this disorder in all its severities, as currently the milder forms of SDB are often untreated. Methodologies used to assess autonomic function in children with SDB include blood pressure (BP), BP variability, baroreflex sensitivity, heart rate variability, peripheral arterial tonometry and catecholamine assays. The aim of this review was to summarise the findings of paediatric studies to date and explore the relationship between autonomic dysfunction and SDB in children, paying particular attention to the roles of disease severity and/or age. This review found evidence of autonomic dysfunction in children with SDB during both wakefulness and sleep. BP dysregulation, elevated generalised sympathetic activity and impairment of autonomic reflexes occur in school-aged children and adolescents with SDB. The adverse effects of SDB seem somewhat less in young children, although more studies are needed. There is mounting evidence that the cardiovascular and autonomic consequences of SDB are not limited to those with OSA, but are also evident in children with PS. The severity of disease and age of onset of autonomic consequences may be important guides for the treatment of SDB.

Introduction

Sleep disordered breathing (SDB) is a common disorder of childhood which ranges in severity from primary snoring (PS) to obstructive sleep apnoea (OSA). OSA affects 1–5% of children[1] and is characterised by prolonged partial and/or intermittent complete upper airway obstruction which disrupts normal ventilation and sleep patterns.[2] Occurring in 3–15% of children,[3] PS describes snoring without associated gas exchange abnormalities or sleep disruption. Despite differences in aetiology, SDB in both adults and children is associated with a number of negative outcomes, including autonomic and cardiovascular dysfunction (for reviews, see[4–10]). In adults there is a dose–response relationship between SDB severity (including snoring) and blood pressure (BP) levels,[11] but this association is less well described in children. In this review we will explore the relationship between autonomic dysfunction and SDB in children, paying particular attention to the influences of disease severity and/or age.

Autonomic control of heart rate and blood pressure in healthy children

The autonomic nervous system (ANS) plays a major role in homeostasis. The two divisions of the ANS, the parasympathetic nervous system and sympathetic nervous system, innervate similar organs but have opposing effects, and thus different outcomes are effected by a shift in the balance of the two systems. The cardiovascular system in particular is highly regulated by the ANS. Parasympathetic neurons innervate the heart, whilst sympathetic efferents innervate blood vessels, the heart, kidneys and adrenal medulla.[12] Parasympathetic activation slows heart rate (HR) through the vagus nerve, and has a rapid response time,[13] whilst sympathetic activation occurs more slowly and acts to increase HR.[14] Alongside HR, the ANS also determines BP through its control of cardiac output and vascular resistance.[12] Tight, short-term control of BP is effected by both parasympathetic and sympathetic

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Abbreviations

ABP	ambulatory blood pressure
ANS	autonomic nervous system
AHI	apnoea hypopnoea index
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BPV	blood pressure variability
BRS	baroreflex sensitivity
CI	confidence interval
DBP	diastolic blood pressure
ECG	electrocardiogram
HF	high frequency power
HR	heart rate
HRV	heart rate variability
LF/HF	low frequency to high frequency ratio
LF	low frequency power
MBP	mean blood pressure
MS	moderate-severe
NREM	non-rapid eye movement sleep
OAI	obstructive apnoea index
OAHI	obstructive apnoea hypopnoea index
OSA	obstructive sleep apnoea
PAT	peripheral arterial tonometry
pNN50	number of pairs of adjacent R–R intervals that differ in length by more than 50 ms
PS	primary snoring
PSG	polysomnography
PTT	pulse transit time
RDI	respiratory disturbance index
REM	rapid eye movement
SBP	systolic blood pressure
SDB	sleep disordered breathing
SpO_2	oxygen saturation
SWS	slow wave sleep

systems through the feedback loop of the baroreflex. Increases in arterial pressure are offset by a reduction in HR, leading to restoration of BP. Conversely, decreases in arterial pressure, or activation of chemoreceptors by hypoxia or hypercapnia, activate the baroreflex mechanisms resulting in increased HR and restoration of normal BP levels. This reflex can be actively reset to adjust to prolonged low or high BP as needed, for example with certain behaviours such as exercise. Baroreceptor resetting may also occur with cardiovascular disease and hence plays a role in the development of prolonged hypertension, as is associated with SDB in adults.[6] Decreased baroreceptor sensitivity leads to increased sympathetic activation, whilst conversely, prolonged raised sympathetic activity can result in attenuated baroreceptor sensitivity.[15] Also part of the sympathetic response, the adrenal glands react to stress (such as hypoxia or hypotension) by releasing catecholamines directly into the circulation, with the effect of redistribution of blood flow through the chronotropic and inotropic effects on the heart.[7]

Normal development of autonomic control of heart rate and blood pressure during childhood

HR and BP are the most common and easily assessed clinical indicators of autonomic function. Beat-by-beat HR can be measured non-invasively through an electrocardiogram (ECG). HR decreases during childhood; from age 5 to 18 y mean 24 h HR has been shown to reduce by 18 bpm in boys (92–74 bpm) and 15 bpm (93–78 bpm) in girls.[16] In contrast, systolic BP (SBP) increases with age,[16,17] whilst diastolic BP (DBP) increases slightly[17] or does not change with age.[16] BP is furthermore affected by body size and gender. In infants and toddlers, an increase in height of 30 cm was associated with a SBP and DBP increase of 10 mmHg.[18] A study of children and adolescents aged 5–21 y showed a slight but significant increase in SBP with height, which was more pronounced in boys than in girls.[19] SBP has been independently correlated with age, height and obesity, whilst in contrast DBP was reported to be independent of age and height and only weakly associated with obesity.[16] Gender differences in BP were apparent in children older than 11 y or of a height greater than 140 cm[16]; but were not apparent in younger children.[16,18,20]

BP can be measured non-invasively at a single point in time (clinic BP), intermittently over 24 h (ambulatory BP (ABP) monitoring) or continuously beat-by-beat through devices commonly worn on the finger. Interpretation of ABP monitoring requires the definition of day (wake) and night (sleep), of which the standard definitions are day-time as 8 AM to 8 PM and night-time as midnight to 6 AM. Wake and sleep periods are difficult to define in young children due to day-time napping and periods of wakefulness overnight. Parent-reported nap-time was associated with a day-time dip in BP in children aged 3–6 y.[20] The degree of change in BP from wake to sleep, referred to as nocturnal dipping, increases with increasing age.[18–20] The mean decrease in SBP and DBP was 3–6% and 3–11% respectively in infants aged 2–3 mo,[18] 8–10% and 16–18% in children aged 3–6 y,[20] and 13% and 23% in children aged 5–21 y[19]; the latter demonstrated dipping independent of height.

Normative BP values expressed as percentiles or z-scores, based on gender, age and height are published for clinic BP during wakefulness.[17,21–23] Normative values are also available specifically for ABP monitoring for day- and night-time periods and across 24 h, based on studies of German children aged 5–21 y.[16,19] No normative BP values are available specific to sleep states or stages, nor for continuous BP measurement. Measures of coupling between spontaneously occurring parallel fluctuations in BP and heart period increased with age in subjects aged 7–22 y, reaching a peak in adolescence.[24] This increase occurred despite a gradual decline in carotid artery elasticity, thus indicating an improvement in cardiovagal function with age.[24]

Oscillations in HR and BP occur over a 24 h period, and include fast changes lasting seconds as well as slower variations over minutes or hours.[12] Fluctuations in HR and BP, that is heart rate variability (HRV) and blood pressure variability (BPV), can be measured using beat-to-beat recordings of HR and BP respectively. HRV and BPV are commonly measured through time-domain and frequency-domain analyses.[25,26] Time-domain parameters are generally reflective of parasympathetic activity, and include measurements such as the number of pairs of adjacent R–R intervals of the ECG that differ in length by more than 50 ms (pNN50) for HRV,[25] and analysis of adjacent pulse intervals for BPV. The differences in speed of action of the parasympathetic and sympathetic nervous systems mean that the divisions operate at different frequencies. Frequency-domain HRV and BPV analysis, or power spectral density analysis, delineates the power within the low frequency (LF) and high frequency (HF) ranges of the HR and BP recordings.[25,27,28] The HF component is related to respiration (respiratory sinus arrhythmia) and thus reflects parasympathetic activity. The LF component of HRV measures a combination of sympathetic and parasympathetic activity, as mediated through the

baroreflex.[25,27,28] The LF/HF ratio is indicative of the sympathovagal balance.[25,26] Studies conducted in children aged 3 d to 15 y have demonstrated that HRV does not simply reflect overall HR, but depends on the age-related flexibility of the ANS.[29,30] The LF/HF ratio decreases from infancy to childhood.[31] LF, HF and total power generally increase from birth until 6 y of age, and then progressively decline from 6 y through adolescence.[31,32] However one study of male children reported an increase in LF power and the LF/HF ratio from 6 y until 12 y of age.[33]

Catecholamine assays of the urine or serum provide a simple indication of generalised autonomic activity. Levels of catecholamines such as noradrenaline (norepinephrine), adrenaline (epinephrine), dopamine and their metabolites normetadrenaline (normetanephrine) and metadrenaline (metanephrine), are indicative of generalised sympathetic activity over the collection time period.[7] Another measure of cardiovascular control is that of baroreflex sensitivity (BRS). BRS can be investigated through spontaneous sequence analysis[34] and cross-spectral analysis[35] of continuous BP and HR measurements. Increasing age is associated with decreased BRS,[36] and lower levels of catecholamines and their metabolites.[37] This suggests decreasing sympathetic and increasing parasympathetic activity throughout childhood. There is a general consensus that maturation of the ANS occurs with increasing age and peaks in adolescence.

Sleep–wake variations in the autonomic regulation of heart rate and blood pressure

In healthy adults[38] and children,[39,40] HR and BP decrease from wake to sleep, are lowest during slow-wave sleep (SWS) and increase during rapid eye movement (REM) sleep. In adults HR and BP are more variable during REM sleep than during non-rapid eye movement (NREM) sleep.[38] A nocturnal dip of HR and BP, of at least 10% in adults, occurs primarily as a result of sympathetic withdrawal and increased parasympathetic tone.[41]

Akin to HR and BP, measures of autonomic activity differ from wake to sleep and throughout the stages of sleep. Sympathetic activity can be measured directly through microneurography, as described in adults, involving microelectrode insertion into nerve fascicles of peripheral muscles.[38] In adults, muscle sympathetic neuronal activity during NREM sleep is reduced to less than half that of wakefulness,[38] leaving parasympathetic activity to predominate. Conversely, REM sleep is punctuated by bursts of sympathetic activity resulting in surges of BP and HR.[38] Non-invasive methods of autonomic assessment are more commonly used however, particularly for investigation in children. For example, HRV can be assessed using Poincaré plots, which demonstrate the beat-to-beat patterning of HR whereby each datum point represents the difference between successive beats.[42,43] In children, Poincaré plots have shown a reduced overall range and variability in HR during SWS sleep compared to during REM and NREM2 sleep.[42] Studies of healthy children have associated SWS sleep with the lowest level of LF power and the highest level of HF power.[39,44–46] The LF/HF ratio decreases during SWS sleep and increases during REM sleep.[44–47] Indeed the strong influence of sleep stage on HRV remains evident even in the context of paediatric SDB.[44–46]

Very few studies have investigated BRS and BPV in children. Studies of healthy children aged 7–13 y demonstrated increased overnight BRS, indicating a shift towards parasympathetic predominance during sleep.[48,49] BRS increases progressively with sleep period time,[48,49] a physiological phenomenon which is not affected by sleep stage.[50] Conversely, sleep stage has a significant effect on BPV; LF BPV is highest during REM sleep and lowest during SWS sleep, whilst HF BPV tends to be lower during REM sleep compared with other sleep stages.[50]

Autonomic control of heart rate and blood pressure in children with sleep disordered breathing

Over the past 15 y, interest in the paediatric consequences of SDB has risen exponentially. In 2005, a meta-analysis conducted by Ng and colleagues[51] found a significant association between SDB and raised BP, whilst another conducted by Zintzaras and colleagues[52] in 2007 found no such evidence. In 2008, the meta-analysis of Ng and co-workers was updated; children with a high apnoea hypopnoea index (AHI) had a significantly higher risk of hypertension (odds ratio 3.15, 95% confidence interval (CI) 2.01–4.93).[53] The following is a review of studies (excluding those assessing the effect of treatment; for review, see[54]) investigating BP and autonomic abnormalities in paediatric SDB. We seek to address whether the cardiovascular consequences of SDB in children are age dependent, and/or severity dependent.

Heart rate variability in children with sleep disordered breathing

Studies reporting HRV during wake and/or sleep in children with SDB are highlighted in Table 1. An early study conducted by Aljadeff and colleagues[43] used Poincaré plots of HR during sleep in seven snoring children (mean obstructive apnoea index (OAI) of zero) and seven children with severe OSA (mean OAI 20 events/h). Children with OSA had significantly reduced beat-to-beat variation at fast and intermediate heart rates, but significantly enhanced variation at slow heart rates. Baharav and colleagues[44] compared frequency-domain variations in HR in snoring children to those with OSA. The authors extended their LF spectrum range (0.02–0.15 Hz) and adjusted indices by mean HR squared before normalising LF and HF power by total power. Results were obtained from epochs which included respiratory events. During wake and all sleep stages, children with OSA had generally higher normalised LF power and LF/HF ratio and lower normalised HF power than children with PS. More recently, analysis of HRV during 1 h of wakefulness identified significantly reduced pNN50 in children with OSA (mean AHI 7 events/h) compared to snoring children without OSA (mean AHI 0.5 events/h).[55] In general, both time- and frequency-domain parameters were reduced in children with OSA, whilst the LF/HF ratio was higher in the OSA group. The lack of a significant group difference may be explained by the reduced severity of OSA in this study compared to earlier studies[43,44] or by the length and/or timing of measurement.

Liao and colleagues[56] reported overnight HRV in a community sample of 616 children, in addition to 43 clinically-referred children with moderate SDB. HRV results were similar between the community-based and clinic-based moderate SDB groups, despite differences in their mean AHI (6 events/h, range 5–7; 26 events/h, range 5–125 respectively). Children with moderate SDB had significantly lower HF power and higher LF/HF ratio than the mild SDB or no-SDB groups, after removing epochs with respiratory events and adjusting for possible confounders including age, race and body mass index (BMI) percentile. The authors concluded that SDB is associated with impaired cardiac autonomic modulation in the sense of sympathetic overflow and weaker parasympathetic modulation. Liao and colleagues[46] then published HRV results specific to sleep stage, in the same community sample of children. Mimicking their previous findings over the whole night, HRV parameters within each separate sleep stage (Wake, NREM2, SWS, REM sleep) were generally lower in the moderate SDB group than in the no-SDB group. The patterns of HRV between wake and sleep stages were generally similar in all groups; however the shift in HRV from SWS to REM sleep, expressed as percentage difference, was more pronounced in the moderate SDB group compared to the no-SDB group, suggesting a greater reduction in parasympathetic

Table 1
Summary of studies of heart rate variability in children with sleep disordered breathing.

Reference	Age range, y (mean ± SE)	Subjects: *n* (definition)	HRV method (timing); epoch length; ECG sampling rate	Study findings
Aljadeff et al., 1997[43]	2–8 (5) PS, 1–6 (5) OSA	7 PS (snoring, normal PSG), 7 OSA (abnormal PSG) [criteria not stated]	Poincaré plots (S)	Reduced beat-to-beat variation in OSA
Baharav et al., 1999[44]	5–14 (6) control, 3–8 (6) OSA	10 Symptomatic control (RDI ≤ 2), 10 OSA (RDI > 2)	Frequency-domain HRV (W & S); 256 s; 200 Hz	Increased LF and LF/HF, reduced HF in OSA
Liao et al., 2010[56]	(9 ± 2)	450 No-SDB (AHI < 1), 159 mild SDB (5 > AHI > 1), 7 community moderate SDB (AHI ≥ 5), 43 clinical moderate SDB (AHI ≥ 5)	Time- & frequency-domain HRV (W & S); 300 s; 100 Hz	Decreased HF and increased LF/HF in moderate SDB groups
Liao et al., 2010[46]	(9 ± 2)	450 No-SDB (AHI < 1), 159 mild SDB (5 > AHI > 1), 7 community moderate SDB (AHI ≥ 5)	Time- & frequency-domain HRV (W & S); 300 s; 100 Hz	Greater shift in HRV from SWS to REM sleep in moderate SDB
Kwok et al., 2011[55]	2–16 (10)	51 Non-OSA (AHI ≤ 1.5, snoring), 40 OSA (AHI > 1.5)	Time- & frequency-domain HRV (1 h W); [length not stated]; 128 Hz	Reduced pNN50 in OSA; no group difference in other parameters
Walter et al., 2012[45]	7–12	20 Controls (OAHI ≤ 1, non-snoring), 20 PS (OAHI ≤ 1, snoring), 20 mild OSA (5 ≥ OAHI > 1), 20 MS OSA (OAHI > 5)	Frequency-domain HRV (W & S); 120 s; 512 Hz	Decreased LF and HF during REM sleep in all SDB groups
Nisbet et al., 2013[93]	3–6 (4)	38 Control (OAHI ≤ 1, non-snoring), 74 PS (OAHI ≤ 1, snoring), 39 mild OSA (5 ≥ OAHI > 1), 29 MS OSA (OAHI > 5)	Time- & frequency-domain HRV (W & S); 120 s; 512 Hz	Increased HF and decreased LF/HF in MS OSA

AHI, apnoea hypopnoea index (events/h); ECG, electrocardiogram; HF, high frequency power; HRV, heart rate variability; LF, low frequency power; MS, moderate–severe; OAHI, obstructive apnoea hypopnoea index (events/h); OSA, obstructive sleep apnoea; pNN50, number of pairs of adjacent R–R intervals that differ in length by more than 50 ms; PS, primary snoring; PSG, polysomnography; RDI, respiratory disturbance index (events/h); REM, rapid eye movement; S, sleep; SDB, sleep disordered breathing; SE, standard error; SWS, slow wave sleep; W, wake.

modulation from SWS to REM sleep in children with moderate SDB. These results however should be interpreted with caution, as the moderate SDB group consisted of only seven children. Additionally, the ECG sampling rate was very low, at 100 Hz (>500 Hz is recommended[25]), although the authors did employ techniques to overcome this. Rather unusually, their mild SDB group showed increased HRV rather than decreased HRV in both overnight[56] and sleep stage specific studies.[46] The authors postulated that the severity and duration of SDB may not be sufficient to noticeably impact the autonomic modulation among the mild SDB group, or, the mild SDB group may be demonstrating a shift towards more efficient autonomic modulation in order to counter the adverse impact of SDB.

Studies of similar methodology, conducted in school-aged[45] and preschool-aged cohorts[93] compared HRV in children with SDB to non-snoring children and demonstrated similar sleep stage patterns of HRV indices in all groups, irrespective of severity. In school-aged children, absolute total, LF and HF power during REM sleep were reduced in all SDB severities compared to control children.[45] Additionally, the LF/HF ratio during SWS was reduced in the moderate–severe (MS) OSA group compared to the PS and control groups. These group differences remained when respiratory events and arousals were excluded from the analysis. In contrast, the absolute total, LF and HF power were significantly higher in the preschool children with MS OSA compared to the control, PS and mild OSA groups during NREM1/2 sleep, and significantly higher in the MS OSA group compared to controls during REM sleep.[93] Furthermore, the LF/HF ratio during SWS sleep was reduced in the MS OSA group compared to the PS and control groups. When respiratory events and arousals were excluded, LF power was similar between control and MS OSA groups in all sleep stages, whilst the group differences in total and HF power and LF/HF ratio remained. It is likely that the increased HRV in preschool children with OSA was due to high frequency fluctuations in HR which occur with increased respiratory effort both during and between respiratory events. However at the school-age, this normal response is dampened due to autonomic dysfunction.[45] A shorter duration of exposure may explain the differing results between ages.

In summary, the interplay between SDB severity and age has been demonstrated in studies of HRV. Reduced HRV during wake and sleep has been repeatedly observed in children with more severe OSA, suggesting altered cardiac autonomic control, whilst PS does not appear to be associated with alterations in HRV. However, preschool children with MS OSA experience increased HRV, likely as a result of increased respiratory effort. Together these studies indicate that age may be an important determinant of the onset of cardiovascular autonomic dysfunction. Further studies are needed to address the impact of age on the maintenance and development of autonomic dysfunction and whether younger children are a more amenable target for treatment.

Blood pressure in children with sleep disordered breathing

Methodology varies greatly between studies in terms of SDB severity and control group definitions and BP measurement, as described in Table 2. Of the studies which reported wake clinic BP alone,[57–63] half reported normalised BP data.[57,62,63] Of the studies recording BP during sleep, comparisons were made with either normative wake clinic BP values[64–67] or night-time ABP norms.[68–73] The use of clinic BP normative values to classify ABP values leads to the over-diagnosis of day-time hypertension and under-diagnosis of night-time hypertension.[74] Whilst the normative ABP values in children were calculated based on a definition of day-time as 08:00 to 20:00 h and night-time as midnight to 06:00 h, varying definitions continue to be used in the literature, based on polysomnography (PSG) scoring,[40,66,67,69,71,72,75] sleep diaries[64,68,70] or clock cut-offs with a transition period of exclusion with[65] and without[73] actigraphy validation. The definition of day-time and night-time has been shown to influence the interpretation of ABP monitoring in children, leading to significant differences in mean BP levels calculated and possible misclassification of hypertension status.[76]

Community-based studies of blood pressure in children with sleep disordered breathing

The majority of community-based studies measured clinic BP during wakefulness. The Tucson Children's Assessment of Sleep

Table 2
Summary of studies of blood pressure in children with sleep disordered breathing.

Reference	Age range, y (mean ± SE)	Subjects: *n* (definition)	BP method (frequency)	Study findings
Community-based				
Enright et al., 2003[57]	6–11 (9)	239: Cohort mean RDI 2% 2.3	Auscultatory (triplicate seated W)	RDI2% associated with elevated BP
Kaditis et al., 2005[60,a]	4–14	50 HS (snoring > 3 nights/wk), 710 non-HS (snoring ≤ 3 nights/wk)	Oscillometric (triplicate morning W)	Snoring did not predict BP
Bixler et al., 2008[58]	5–12	517 No SDB (AHI < 1), 175 mild SDB (5 > AHI > 1), 8 moderate SDB (AHI ≥ 5)	Oscillometric (triplicate seated W)	Elevations in SBP associated with step-wise increases in AHI
Li et al., 2008[72]	6–13	127 Control (AHI < 1, snoring < 3 nights/wk), 133 mild OSA (AHI 1–5), 46 MS OSA (AHI > 5)	<24 h ABP (W 30 min, S 60 min)	Higher BP z-scores in MS OSA
Li et al., 2009[71]	6–13	56 Control (AHI < 1, snoring< 3 nights/wk), 46 PS (AHI < 1, snoring ≥ 3 nights/wk), 88 OSA (62 AHI 1–3; 26 AHI > 3)	<24 h ABP (W 30 min, S 60 min)	Increasing trend in BP z-scores across the SDB spectrum
Marshall et al., 2011,[61,a]	8	409: 166 snored (52 < 1 night/wk; 38 >1 night/wk; 28 > 3 nights/wk; 48 every night)	Oscillometric (triplicate supine W)	No association between snoring and BP
Archbold et al., 2012[62]	10–18 (14)	334: Cohort mean RDI3% at baseline 1.1, at 5 y follow-up 0.6	Auscultatory (triplicate seated W)	Decreased TST associated with increased SBP
Clinical sample				
Marcus et al., 1998[66]	(8 ± 4 PS, 5 ± 3 OSA)	26 PS (OAI ≤ 1), 41 OSA (OAI > 1)	Oscillometric (supine W & S 15 min)	Higher DBP in OSA
Kohyama et al., 2003[67]	4–11	23 SDB: 16 AHI ≥ 10, 7 AHI < 10	Oscillometric (supine W & S 15 min)	Higher BP indices during W and REM in higher AHI group
Kwok et al., 2003[59]	(10 ± 3)	30 Control (questionnaire only), 30 PS (AHI ≤ 1)	Oscillometric (duplicate seated W)	Higher BP in PS
Amin et al., 2004[64]	5–17 (11)	21 PS (AHI ≤ 1), 17 mild OSA (5 > AHI > 1), 22 MS OSA (AHI > 5)	24 h ABP (W & S 15 min)	No group differences in sleep BP; decreased W DBP and smaller MBP dip in OSA
Guilleminault et al., 2004[63]	7–12	Retrospective: 30 control, 271 SDB. Prospective: 70 SDB, 8 SDB 'BP outliers'	[Method not stated] Seated W	Group differences in BP
Leung et al., 2006[69]	6–15 (9)	96 SDB: 79 AHI ≤ 5, 17 AHI > 5	24 h ABP (W 15 min, S 30 min)	Increased sleep BP indices and BP load in high AHI group
Amin et al., 2008[65]	7–13	140: Control (AHI < 1, no snoring), mild SDB (5 > AHI > 1), severe SDB (AHI > 5)	24 h ABP (W & S 15 min)	Increased DBP and MBP during W and S, increased BP load in MS OSA
Kirk et al., 2010[70]	4–15 (9)	30 OSA (AHI > 1.5)	24 h ABP (W 20 min, S 30 min)	Increase in BP percentile unit associated with increase in AHI
Horne et al., 2011,[40] 2013[77]	7–13	36 Control (OAHI ≤ 1, no snoring), 61 PS (OAHI ≤ 1, snoring), 23 mild OSA (5 ≥ OAHI > 1), 21 MS OSA (OAHI > 5)	Finometer™ (continuous supine W & S)	Elevated BP during W and S in all SDB severities; preserved dipping in all SDB severities
Weber et al., 2012[68]	8–12	12 PS (AHI < 4 or AI < 1), 14 OSA (AHI ≥ 4 or AI ≥ 1)	24 h ABP (W 15 min, S 30 min)	Decreased dipping in OSA
Xu et al., 2012[73]	5–14	38 Non-OSA (snoring, AHI ≤ 5 or OAI ≤ 1), 107 OSA (AHI > 5 or OAI > 1)	24 h ABP (W 30 min, S 60 min)	Increased BP indices during S and decreased dipping in OSA
Nisbet et al., 2013[75]	3–6	35 Control (OAHI ≤ 1, no snoring), 66 PS (OAHI ≤ 1, snoring), 34 mild OSA (5 ≥ OAHI > 1), 28 MS OSA (OAHI > 5)	PTT (continuous supine W &S)	Decreased PTT (elevated BP) during REM in MS OSA

ABP, ambulatory blood pressure; AHI, apnoea hypopnoea index (events/h); AI, apnoea index (events/h); BP, blood pressure; DBP, diastolic BP; HS, habitual snoring; MBP, mean blood pressure; MS, moderate-severe; OAHI, obstructive apnoea hypopnoea index (events/h); OAI, obstructive apnoea index (events/h); OSA, obstructive sleep apnoea; PS, primary snoring; PTT, pulse transit time; RDI, respiratory disturbance index (events/h); RDI2%, number of apnoeas and hypopnoeas associated with a 2% oxygen desaturation per hour of sleep; RDI3%, number of apnoeas and hypopnoeas associated with a 3% oxygen desaturation per hour of sleep; REM, rapid eye movement sleep; S, sleep; SBP, systolic blood pressure; SDB, sleep disordered breathing; SE, standard error; TST, total sleep time; W, wake.

[a] Questionnaire only studies – all other studies involve PSG (usually lab-based).

Apnoea Study described the associations between SDB and elevated resting BP in children aged 6–11 y at baseline,[57] and at 5 y follow-up.[62] At baseline, obesity, sleep efficiency and respiratory disturbance index (RDI) 2% (number of apnoeas and hypopnoeas associated with a 2% oxygen desaturation per hour of sleep) were independently associated with elevated SBP and DBP.[57] At follow-up, change in obesity status and a decrease in the total sleep time were associated with increases in SBP, more so than the effect of SDB.[62] The largest community study recorded wake clinic BP at the time of PSG in 700 children.[58] Elevations in SBP were associated with step-wise increases in AHI (AHI ≥ 1, 2.9 mmHg; AHI ≥ 3, 7.1 mmHg; AHI ≥ 5, 12.9 mmHg), which remained significant after adjusting for age, sex, race, BMI percentile or waist circumference, sleep efficiency, percentage of REM sleep and snoring status. Importantly, this study assessed both subjective (parent-report) and objective (PSG) snoring in relation to BP. Within the mild SDB group, those with objectively measured snoring (37%) had significantly higher DBP and mean BP (MBP) than non-snorers with mild SDB, suggesting that snoring in the presence of mild SDB may be associated with an additional risk for elevated BP. Subjectively measured snoring was not associated with increases in BP. This may explain why a study of parent-reported snoring in 8 y old children found no association with BP.[61] Another questionnaire-based study, of Greek children aged 4–14 y, found age, gender and BMI to be significant predictors of wake clinic SBP and DBP, whilst snoring (>3 nights/wk) was not.[60] The lack of PSG to objectively quantify SDB severity is a major limitation to these studies.

Two community-based studies used ABP monitoring and lab-based PSG to assess BP and SDB in children aged 6–13 y from randomly selected schools.[71,72] Group comparisons were made between children with mild OSA, MS OSA and controls (snoring <3 nights/wk).[72] Children with MS OSA had significantly higher

wake and sleep z-scores for SBP, DBP and MBP than controls, and significantly higher wake z-scores for SBP, DBP and MBP than children with mild OSA. There were no group differences regarding nocturnal dipping of BP. Adjusted for age, gender, BMI and waist circumference, the MS OSA group had a significantly higher risk of sleep systolic and diastolic hypertension than controls (odds ratio 3.9 (95% CI 1.4–10.5), 3.3 (95% CI 1.4–8.1) respectively), but this increased risk was not seen in the mild OSA group. Analyses were repeated in children ≤ 85th percentile for weight (non-overweight), and similar group differences in BP patterns were seen, demonstrating that the effect of OSA on BP elevation was independent of obesity in this cohort. A second study by this group[71] incorporated the full spectrum of SDB, and found evidence of BP abnormalities in children with all severities of SDB. During both wake and sleep, z-scores for SBP, DBP and MBP all exhibited an increasing trend across the severity spectrum. The proportion of MBP non-dippers also increased across the groups. Of note, children with PS had a significantly higher sleep DBP z-score than controls.

Studies of blood pressure in a clinical sample of children with sleep disordered breathing

Marcus and colleagues[66] were the first to report clinic BP in children with PS and OSA, measured every 15 min during wake and sleep. Children with OSA had higher wake and sleep DBP indices (calculated from wake clinic BP norms[21] as none were available for sleep) than those with PS, whilst SBP indices were similar between groups. In a similar manner, clinic BP was measured during wake and sleep in children with low AHI (mean 4 events/h, range 0–9.5) and high AHI (mean 27 events/h, range 12–52).[67] SBP and DBP indices during wake and REM sleep were significantly higher in the more severe group, although there were no group differences during NREM sleep. Kwok and co-workers[59] measured wake clinic BP in children with PS compared to non-snoring (parental questionnaire) control children of matched age and BMI. Compared to controls, children with PS had significantly higher unadjusted SBP, DBP and MBP, and reduced arterial distensibility, measured through pulse wave velocity.

Children with SDB can also exhibit low BP. Children with low wake clinic BP (SBP/DBP <85/60 mmHg) were identified both retrospectively and prospectively.[63] Significant differences in unadjusted SBP and DBP were seen between the low BP SDB group, a normotensive SDB group (matched for AHI) and a non-snoring control group. Interestingly, BP levels of the normotensive SDB group were significantly higher than BP levels in non-snoring controls.

The first study to record ABP in children with SDB, conducted by Amin and colleagues,[64] compared 21 children with PS to 39 children with OSA. Children with OSA had significantly greater mean BPV during wake and sleep, in addition to a smaller nocturnal MBP dip. There were no group differences in sleep SBP, DBP or MBP. The lowest wake DBP occurred in the highest AHI group for both absolute and indexed values (using wake clinic BP norms). The authors suggest these findings represent abnormal elastic recoil of blood vessels during diastole which could indicate the early stages of autonomic and/or endothelial dysfunction. A second study by the same group[65] compared children with mild and MS OSA to non-snoring controls and found a dose-dependent increase in BP with increasing SDB severity. DBP, MBP and HR during wake and sleep were significantly higher in the MS OSA group compared to controls. A group difference was seen for wake SBP but not for sleep SBP. The morning BP surge and also BP loads (defined as the percentage of BP readings which exceed the 95th percentile of normal ABP for gender and height) across 24 h and wake, were significantly higher in children with MS OSA than in controls. The mild OSA group also had a higher morning SBP surge than controls, in the absence of significant elevation of nocturnal and diurnal BP. A smaller study reported ABP without normalisation and found children with OSA to have decreased nocturnal dipping of DBP and MBP than children with PS.[68] 16% (2/12) of children with PS were non-dippers (mean nocturnal decline in BP of <10%) compared to 57% (8/14) of children with OSA. In contrast, a study of continuous BP measurement in children aged 7–13 y reported preserved nocturnal dipping in all severities of SDB (PS, mild OSA, MS OSA) in comparison to non-snoring controls.[77] The mean decline in BP from wake to all stages of sleep was similar in all groups and furthermore there were no group differences in proportions of dippers and non-dippers.

Leung[69] and colleagues reported 24 h ABP, adjusted for ABP norms, in snoring children aged 6–15 y and compared subjects with an AHI ≤ 5 events/h to those with an AHI > 5. The indices for wake SBP, sleep SBP and sleep DBP were significantly increased in the higher AHI group, as were the sleep SBP and DBP loads. However BMI z-score was significantly larger in the highest AHI group. Of the entire cohort, 16 (17%) children were hypertensive (BP >95th percentile of ABP norms for gender and height): 11 were nocturnally hypertensive only and five had 24 h hypertension; six had systolic hypertension only, five had diastolic hypertension only and five had both systolic and diastolic hypertension. All hypertensive children were non-dippers or reverse-dippers (mean nocturnal BP higher than mean day-time BP), however the proportion of non-dippers was similar in both AHI groups. A smaller study of 30 children with PSG-defined OSA reported pre-hypertension (high clinic BP with normal 24 h ABP) in three (10%) children, and masked hypertension (normal clinic BP with a high 24 h ABP) in seven (23%) children, of which all ten had elevated nocturnal SBP whilst five had additionally elevated day-time SBP.[70] After adjustment for BMI percentile, the authors demonstrated an increase in BP percentile units per unit increase in AHI, night-time DBP 1.16 percentile units, night-time SBP 1.96 percentile units, day-time DBP 1.21 percentile units. Another ABP study reported children with OSA to have significantly higher mean night-time SBP and DBP indices, increased BP load, and decreased nocturnal BP dipping in comparison to non-OSA children of similar age and BMI.[73] Group differences were reported despite the non-OSA group having a mean AHI of 1.8 events/h, which some studies would classify as OSA.

Beat-to-beat changes in BP during sleep have been recorded in three studies of children with SDB in comparison to non-snoring control children.[40,49,75] McConnell and colleagues[49] found SBP and DBP, averaged over the whole night, to be significantly higher in school-aged children with mild and severe OSA than in control children. Horne and colleagues[40] reported BP according to sleep stage and found that school-aged children with PS, mild OSA and MS OSA demonstrated elevated BP by 10–15 mmHg in comparison to control children during wake before sleep onset, NREM1/2 and NREM3/4 and REM sleep. Results were unchanged when respiratory events were removed, demonstrating that significant alterations in BP occur even during stable sleep. In children under 5 y, cuff sizes for continuous measurement are limited and compliance with ABP is difficult. An alternative method of continuously assessing BP is that of pulse transit time (PTT), which can provide an inverse measurement of changes in BP.[78] As BP increases, arterial wall stiffness increases and the pulse-wave propagates faster thereby decreasing the PTT. PTT is calculated as the time delay between the ECG R-wave and a pre-determined point on the corresponding pulse wave typically measured at the finger. A study using PTT as an indicator of BP changes in preschool-aged children found those with PS, mild or MS OSA were not different from non-snoring controls during NREM1/2 and NREM3/4 sleep, however during REM sleep those with MS OSA had higher BP, as indicated by

decreased PTT.[75] Removal of respiratory events did not alter the PTT findings. The authors suggest that the REM sleep-related BP elevation may be the first step towards more extensive BP abnormalities.

In summary, there is clear evidence for an effect of SDB severity on BP, as demonstrated through both clinic and community-based studies in children. Raised BP during wake and sleep is exhibited not only by children with OSA, but also those with PS. Furthermore some studies have demonstrated BP elevation to the levels of clinical hypertension. However, the influence of age on the association between SDB and BP still needs to be addressed, although studies to date suggest a smaller impact at the preschool age than at the school age. It may be that whilst milder severities of SDB initially escape adverse BP effects, with time this evolves so that even children with PS and mild OSA have measurable cardiovascular risk.

Baroreflex sensitivity and blood pressure variability in children with sleep disordered breathing

Studies investigating the effect of SDB on BRS and/or BPV in children are outlined in Table 3. A community study in adolescents calculated BRS from a 5 min day-time BP recording, and found it to be reduced in adolescents with elevated scores on the Paediatric Sleep Questionnaire, particularly in the presence of a higher BMI.[79] However the prevalence of SDB in this cohort was likely to be low, as the mean score was 0.1 ± 0.01, which is below the score (>0.33) suggested for clinical diagnosis of SDB.[80] Studies in children with SDB aged 7–13 y have reported decreased night-time BRS in children with mild and MS OSA compared to non-snoring control children[49] and children with PS.[50] This pattern occurred over the night as a whole,[49] but also during all sleep stages.[50] Furthermore, the normal progressive increase in BRS over the night seen in control children was still evident in children with mild OSA, but was not seen in children with MS OSA.[49] Both LF and HF SBP variability were significantly higher in children with OSA than in controls, and moreover were significantly higher in the MS OSA group than the mild OSA group.[49] Indeed, children with MS OSA have a 30% increase in LF BPV and a seven-fold increase in HF BPV during sleep compared with controls, and do not demonstrate sleep stage differences.[50] Heart period delay, a measure of the delay in beat-to-beat HR response to changes in BP, was prolonged in children with OSA but also prolonged in children with PS.[50]

In summary, these studies demonstrate that children with OSA exhibit baroreflex impairment, and this reduction in BRS is likely due to alterations in both parasympathetic and sympathetic components of HR control and results in increased BPV. Furthermore children with PS have shown signs of parasympathetic impairment, in the form of a delayed HR response to fluctuations in BP. The influence of age on the relationship between SDB and BRS and BPV is yet to be elucidated.

Autonomic reflex tests in children with sleep disordered breathing

Aside from measuring resting control of HR and BP, autonomic challenge tests can be used to examine the reactivity of the ANS to stimuli. Autonomic challenge tests can elicit either a primarily parasympathetic or sympathetic response, simultaneous activation of both nervous systems, or a shift between the two systems. The Valsalva manoeuvre and deep breathing test reflect cardiac parasympathetic activity.[81] The cold pressor test elicits alpha adrenoreceptor-mediated peripheral vasoconstriction and thus is reflective of sympathetic reactivity.[82] This differs from the cold face stimulation test, which elicits increased peripheral sympathetic activity in association with a bradycardia as a consequence of increased vagal drive.[82] The head-up tilt test induces a physiological fall in BP, which activates peripheral vasoconstriction mediated by sympathetic activity.[81] Additional to changes in BP, the HR response to the tilt is also of interest. HR increases rapidly which is maximal at about beat 15, a relative overshoot bradycardia then occurs, which is maximal at approximately beat 30, this response is mediated by the vagus nerve.[81] Thus the 30:15 index is indicative of autonomic balance.

Studies investigating autonomic reflexes during wakefulness in children with SDB are outlined in Table 4. O'Brien and Gozal[83] recorded peripheral arterial tonometry (PAT) in children during vital capacity sighs and cold pressor testing immediately prior to PSG. PAT uses plethysmography to continuously measure pulsatile volume changes of the digital vascular beds.[84] The PAT signal was significantly attenuated in children with OSA in comparison to controls, indicating increased sympathetic tone during wakefulness.[83] Following the cold pressor test, the recovery dynamics of the control children were much faster, with a return to baseline evident within 4 min in the control children compared to 10 min in children with OSA, demonstrating that children with OSA have altered vascular reactivity. The authors suggested that children with OSA may be unable to down-regulate the sympathetic overactivity induced by the challenge.

Montesano and colleagues[85] conducted autonomic cardiovascular tests (selections from the Ewing test battery[81]) in children with OSA and age-matched controls. No difference in autonomic cardiovascular response was seen with the Valsalva manoeuvre in a study of children with OSA compared to controls, however a smaller change in HR was seen with each respiratory cycle in the OSA group during the deep breathing test, indicating parasympathetic hypoactivity.[85] Additionally, the response to the head-

Table 3
Summary of studies of baroreflex sensitivity and blood pressure variability in children with sleep disordered breathing.

Reference	Age range, y (mean)	Subjects: *n* (definition)	Method [Device] (timing)	Study findings
McConnell et al., 2009[49]	7–13 (10)	50 Control (non-snoring, OI $\leq$ 1), 63 mild OSA (5 $>$ OI $>$ 1), 56 MS OSA (OI $\geq$ 5)	BRS & BPV: time- and frequency-domain analysis [Portapres™] (W & S)	Reduced BRS in OSA; increased LF and HF systolic BPV in OSA
Coverdale et al., 2012[79]	11–14 (12)	106	BRS: frequency-domain & transfer function analysis [Finapres™] (W)	Reduced BRS in questionnaire SDB-positive subjects
Walter et al., 2013[50]	7–13	36 Control (non-snoring, OAHI $\leq$ 1), 61 PS (snoring, OAHI $\leq$ 1), 23 mild OSA (5 $\geq$ OAHI $>$ 1), 21 MS OSA (OAHI $>$ 5)	BRS & BPV: cross-spectral & frequency-domain analysis [Finometer™] (W & S)	Reduced BRS in OSA; increased LF and HF BPV in OSA; prolonged heart period delay in all SDB groups

BRS, baroreflex sensitivity; BPV, blood pressure variability; HF, high frequency power; LF, low frequency power; MS, moderate-severe; OAHI, obstructive apnoea hypopnoea index (events/h); OI, obstructive index (events/h); OSA, obstructive sleep apnoea; PS, primary snoring; S, sleep; SDB, sleep disordered breathing; W, wake.

Table 4
Summary of studies of autonomic challenges in children with sleep disordered breathing.

Reference	Age range, y (mean ± SE)	Subjects: *n* (definition)	Measurement method; challenge (timing)	Study findings
Guilleminault et al., 2004[63]	8–11 (9)	5 Controls (non-snoring), 7 normotensive SDB, 7 hypotensive SDB (bedtime BP < 80/60) [SDB criteria not stated]	Continuous HR & BP (Finapres™); head-up tilt (W)	Larger BP change following tilt in SDB groups
O'Brien and Gozal, 2005[83]	6–17 (10)	29 Controls (AHI < 1, no snoring), 28 SDB (AHI > 5)	PAT; vital capacity sigh, cold pressor test (W)	Attenuated PAT signal and faster recovery dynamics in OSA
Lin et al., 2005[86]	(11 ± 1)	10 Controls, 10 MS OSA [criteria not stated]	HRV & BPV; spontaneous breathing supine & standing, cold face stimulation (W)	Greater increase in LF mean BPV upon standing in OSA
Chaicharn et al., 2009[87]	8–17 (11)	10 Controls (non-snoring, no PSG), 10 MS OSA (AHI ≥ 5)	HRV & BPV; spontaneous breathing supine & standing, cold face stimulation (W)	Smaller change in SBP and BRS in OSA
Montesano et al., 2010[85]	6–17 (11 controls, 9 OSA)	25 Controls (non-snoring, no PSG), 18 OSA (AHI > 1)	Changes in HR & BP (auscultatory); head-up tilt, deep breathing, Valsalva (W)	Smaller HR change during deep breathing and larger BP change following tilt in OSA

AHI, apnoea hypopnoea index; BP, blood pressure (mmHg); BPV, blood pressure variability; BRS, baroreflex sensitivity; HR, heart rate; HRV, heart rate variability; LF, low frequency power; MS, moderate-severe; OSA, obstructive sleep apnoea; PAT, peripheral arterial tonometry; PSG, polysomnography; SBP, systolic blood pressure; SDB, sleep disordered breathing; SE, standard error; W, wake.

up tilt test differed between groups; compared to controls the OSA group demonstrated a larger change in SBP and DBP and lower 30:15 index.[85] The authors concluded that overall, their findings suggested an increase in baseline day-time sympathetic activity in children with OSA, in association with an imbalance of parasympathetic response to acute stimuli. A smaller study which measured BP continuously during head-up tilt tests, similarly found the fall in BP elicited by the tilt to be smallest in the non-snoring control group.[63] Interestingly, the fall in BP was greatest in the hypotensive (as defined by bed-time clinic BP) SDB group and second largest in the normotensive SDB group. Children with SDB demonstrated limited tachycardia with a percentage increase in HR roughly half that of controls.

Model-based assessments of cardiovascular autonomic control in paediatric OSA have reported findings of normal parasympathetic activity despite elevated sympathetic activity.[86,87] Chaicharn[87] and colleagues employed a closed-loop model to relate HRV to respiration and BPV, and relate BPV to changes in HR and respiration so that the confounding effects of respiration from other sources that contribute to HRV and BPV could be eliminated. The mean AHI of the OSA group was 21 events/h (range 5–52), however controls did not undergo PSG. Both control and OSA groups had a bradycardic response to cold face stimulation, with an associated SBP rise; however, the total percentage increase in SBP in children with OSA was only half as large as that in control subjects. BRS was lower in the OSA group compared to controls and whilst it decreased upon standing in both groups, the reduction was smaller in children with OSA.

In summary, children with OSA exhibit abnormal autonomic responses to stimuli during wakefulness, in the forms of elevated sympathetic reactivity and weaker parasympathetic modulation. However to date there have been no autonomic challenge studies conducted in children with PS. Additionally, all studies had a mean subject age of 9, 10 or 11 y, and did not include subjects younger than 6 y, most likely due to the increased difficulty of compliance in younger children. Thus the autonomic response in children with PS to a challenge test is yet to be elucidated, as is the effect of SDB on this autonomic response during early childhood.

Catecholamine levels in children with sleep disordered breathing

Table 5 presents the studies which have assessed overnight or morning serum and/or urinary catecholamine levels in children with varying severities of SDB. Serum noradrenaline and adrenaline were sampled hourly during PSG to investigate the association between SDB and elevated catecholamines in adolescents with metabolic syndrome.[88] The mean hourly noradrenaline levels were higher in those with metabolic syndrome and SDB compared to those without SDB, after controlling for age and BMI z-score.[88] Group differences were also identified by Snow and colleagues,[89] who reported significantly higher morning urinary noradrenaline and adrenaline levels, but not dopamine, in children with OSA compared to snoring children without OSA. Furthering this, blood samples for gene expression assays were drawn within 1 h of awakening in a subsample of 20 OSA and 20 age-, gender-, race- and BMI-matched non-OSA children. Whilst there was no effect of obesity, significant differences between the OSA and non-OSA children were seen in catecholamine-related gene expressions relating to catecholamine production, transport and receptors.

Urinary catecholamines in school-age children with varying severities of SDB have also been investigated in comparison to control groups.[90,91] The first study reported higher noradrenaline levels in the severe hypoxaemia group compared to moderate hypoxaemia or control groups.[91] A second study found that when compared to controls, higher urinary noradrenaline, adrenaline and dopamine levels were observed in children with OSA, whilst no differences were seen with PS.[90] Furthering this, noradrenaline, adrenaline and normetadrenaline levels have been correlated with various indices of SDB severity, including AHI, 4% oxygen desaturation index, oxygen saturation (SpO_2) nadir and the respiratory arousal index.[89–92] In addition, urinary adrenaline[90] has been correlated with SBP and DBP z-scores and normetadrenaline[91] with DBP z-scores. However, a study specifically in preschool children found no differences in urinary catecholamines between control or SDB severity groups, although the obstructive AHI (OAHI) weakly correlated with noradrenaline levels, but not with adrenaline or dopamine levels.[93]

In summary, there is a clear association between elevated catecholamine levels and OSA in children, with greatest evidence for increased noradrenaline levels. However, significantly elevated catecholamine levels in comparison to healthy non-snoring children have yet to be demonstrated in children with PS, which is possibly related to the power of studies. Nevertheless, as there is indication of increasing catecholamines with increasing SDB severity indices, it is likely that children with PS also experience sympathetic activity above normal levels. Such sympathetic activation likely contributes to the BP abnormalities seen in paediatric SDB, as evidenced by the association, albeit preliminary, between

Table 5
Summary of studies of catecholamine levels in children with sleep disordered breathing.

Reference	Age range, y (mean ± SE)	Subjects: *n* (definition)	Catecholamine method	Study findings
Nakra et al., 2008[88]	7–19	25 Metabolic syndrome & SDB (AHI ≥ 1.5), 9 metabolic syndrome & no-SDB (AHI < 1.5)	Serum noradrenaline and adrenaline sampled hourly during 8 h PSG	Increased noradrenaline in SDB
Snow et al., 2009[89]	4–16 (7)	78 Non-OSA (AHI < 1, snoring), 81 OSA (AHI > 1)	Morning urinary noradrenaline, adrenaline, dopamine	Increased noradrenaline and adrenaline in OSA
Kaditis et al., 2009[91]	(7 ± 3 controls, 5 ± 2 severe, 6 ± 2 moderate, 7 ± 2 mild)	10 Controls (non-snoring, no PSG), 12 severe hypoxaemia (SpO_2 nadir ≤ 86%), 20 moderate hypoxaemia (90 > nadir > 86%), 22 mild hypoxaemia (nadir >90%)	Morning urinary noradrenaline, adrenaline, normetadrenaline, metadrenaline	Increased noradrenaline in severe hypoxaemia
Kelly et al., 2010[92]	4–18 (11)	44 Controls (symptomatic, AHI < 1.5), 54 OSA (AHI ≥ 1.5)	24 h urinary noradrenaline, adrenaline, normetadrenaline, metadrenaline	AHI and oxygen desaturation associated with higher noradrenaline and normetadrenaline
O'Driscoll et al., 2011[90]	3–12 (7 controls, 5 SDB)	26 Controls (AHI < 1, non-snoring), 33 PS (AHI ≤ 1, snoring), 20 mild OSA (5 ≥ AHI > 1), 17 MS OSA (AHI > 5)	12 h urinary noradrenaline, adrenaline, dopamine	All catecholamines increased in OSA
Nisbet et al., 2013[93]	3–6 (4)	28 Controls (OAHI ≤ 1, non-snoring), 49 PS (OAHI ≤ 1, snoring), 25 mild OSA (5 ≥ OAHI > 1), 18 MS OSA (OAHI > 5)	12 h urinary noradrenaline, adrenaline, dopamine	No group differences

AHI, apnoea hypopnoea index; MS, moderate-severe; OAHI, obstructive apnoea hypopnoea index; OSA, obstructive sleep apnoea; PS, primary snoring; PSG, polysomnography; SDB, sleep disordered breathing; SE, standard error; SpO_2, oxygen saturation.

BP z-scores and catecholamine levels.[90,91] To date it appears that the association between paediatric SDB and increased catecholamine levels strengthens with age.

Conclusions

Children with SDB exhibit autonomic dysfunction which pervades both wakefulness and sleep. It is apparent that complex readjustment of autonomic homeostatic mechanisms occurs with adult and paediatric SDB alike. BP dysregulation, in the forms of increased BPV and elevated systolic and/or diastolic BP, have been repeatedly demonstrated in school-aged children and adolescents with SDB, alongside elevated generalised sympathetic activity and impairment of autonomic reflexes, particularly that of the baroreflex. There is mounting evidence that the cardiovascular and autonomic consequences of SDB are not limited to those with OSA, but are also evident in children with PS. The adverse effects of SDB seem somewhat less in young children, although more studies are needed in this age group. Longitudinal studies may help elucidate whether exposure to SDB at a young age increases future susceptibility to cardiovascular disease. Future research needs to focus on relating the response to treatment to the age of SDB disease onset, as it may be that whilst some cardiovascular consequences are somewhat reversible, the improvement in morbidity achieved is dependent upon the age at which the insult occurred, and the severity of the exposure.

Practice points

Sleep disordered breathing in children is associated with autonomic dysfunction during wakefulness and sleep, which may include:

- Elevated blood pressure and increased blood pressure variability.
- Abnormal blood pressure control and reduced autonomic reflexes.
- Increased sympathetic activity and decreased parasympathetic activity.

Research agenda

In order to further this research, longitudinal studies are needed to:

- Elucidate whether exposure to sleep disordered breathing at a young age increases future susceptibility to cardiovascular morbidity.
- Relate the response to treatment and improvement in morbidity to the age of sleep disordered breathing occurrence.
- Relate the response to treatment and improvement in morbidity to the degree of sleep disordered breathing severity.

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